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(54) Title: PROCESS TO TETRAHYDROTRIAZOLOPYRAZINES AND INTERMEDIATES

(57) Abstract: A novel process is provided for the preparation of substituted-5,6,7,8-tetrahydro[1,2,4]-triazolo[4,3-α]pyrazines which are useful in the synthesis of dipeptidyl peptidase-IV inhibitors for the treatment of Type 2 diabetes. Also provided are useful intermediates obtained from the process.

WO 2004/080958 A2

23

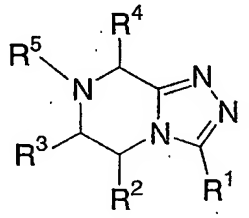
TITLE OF THE INVENTION
PROCESS TO TETRAHYDROTRIAZOLOPYRAZINES AND INTERMEDIATES

FIELD OF THE INVENTION

The present invention discloses a novel process and novel intermediates toward the preparation of substituted-5,6,7,8-tetrahydro[1,2,4]-triazolo[4,3-*a*]pyrazines which are useful in the synthesis of dipeptidyl peptidase-IV (DP-IV) inhibitors.

BACKGROUND OF THE INVENTION

The present invention provides an improved process for the preparation of substituted-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazines of structural formula I



(I)

or an acid salt thereof; wherein
R^1 is optionally substituted phenyl or C_{1-4} alkyl unsubstituted or substituted with one to five fluorines; and
R^2, R^3, R^4 and R^5 are each independently hydrogen, C_{1-4} alkyl, or optionally substituted benzyl; or R^2 and R^3 taken together with the carbon atoms to which they are attached form a 5- to 7-membered cyclic aliphatic ring.

The present invention also provides intermediates useful in the disclosed process.

The synthesis of tetrahydrotriazolopyrazines of structural formula I has previously been described in PCT international patent application WO 03/004498, which published on January 16, 2003. In this publication, the heterocyclic ring was obtained by way of catalytic hydrogenation of [1,2,4]triazolo[4,3-*a*]pyrazines which were prepared following the methodology described by Nelson and Potts in J. Org. Chem., 27: 3243-3248 (1962). This approach involves a total of four chemical steps starting with 2-chloropyrazine, but suffers from numerous disadvantages, not the least of which being the need to use excess hydrazine at elevated temperatures with the attendant risk of explosion.

In the present invention, compounds of structural formula I are produced in an efficient manner in a total of five chemical steps from hydrazine which is used at low

temperature thereby substantially reducing the handling and operational hazards. The present process involves reaction of a C-5 substituted 2-(chloromethyl)-1,3,4-oxadiazole with an appropriately substituted ethylenediamine to generate an amidine intermediate which is then cyclized to afford the desired final product either as a free base or a suitable acid salt thereof. The process of the present invention represents an improved variation of the procedure described in Japan Patent 06128261 (1994) (assigned to Toray Ind., Inc.) for the synthesis of the benzene-fused analogs of the compounds of structural formula I, namely 4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinoxalines. The instant process takes advantage of the enhanced reactivity of ethylenediamines relative to 1,2-phenylenediamines with 2-(chloromethyl)-1,3,4-oxadiazoles.

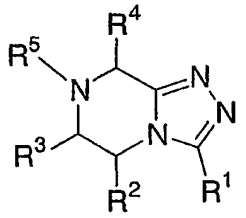
SUMMARY OF THE INVENTION

This invention is concerned with a process for preparing substituted-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazines of structural formula I and certain useful intermediates obtained during that process. The process involves the reaction of an optionally substituted ethylenediamine with a C-5 substituted 2-(chloromethyl)-1,3,4-oxadiazole to generate an amidine intermediate which is then cyclized optionally in the presence of acid or base to afford the desired product. The 2-(chloromethyl)-1,3,4-oxadiazole intermediate is efficiently prepared by cyclodehydration of a bishydrazide intermediate which is prepared by sequential bis-acylation of hydrazine.

As disclosed in WO 03/004498, compounds of structural formula I represent key intermediates in the synthesis of dipeptidyl peptidase-IV (DP-IV) inhibitors which are useful for the treatment of Type 2 diabetes.

DETAILED DESCRIPTION OF THE INVENTION

The process of the present invention involves the preparation of a compound of structural formula I:



(I)

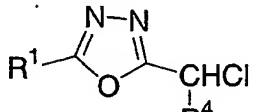
or an acid salt thereof, wherein

R^1 is optionally substituted phenyl or C_{1-4} alkyl unsubstituted or substituted with one to five fluorines; and

R^2, R^3, R^4 and R^5 are each independently hydrogen, C_{1-4} alkyl, or optionally substituted benzyl; or R^2 and R^3 taken together with the carbon atoms to which they are attached form a 5- to 7-membered cyclic aliphatic ring;

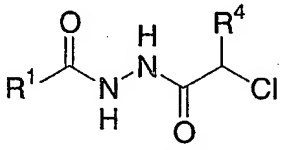
comprising the steps of:

(a) producing a compound of structural formula II:



(II)

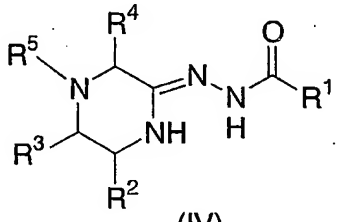
by treating a compound of structural formula III:



(III)

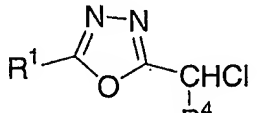
with a dehydration reagent;

(b) producing a compound of structural formula IV:



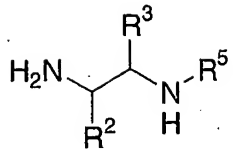
(IV)

by treating a compound of structural formula II:



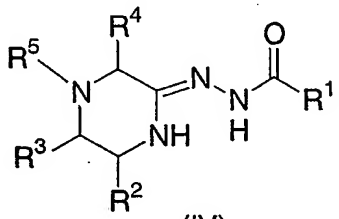
(II)

with an ethylenediamine of structural formula V in a suitable organic solvent



(V) ;

and (c) cyclizing a compound of structural formula IV in a suitable organic solvent



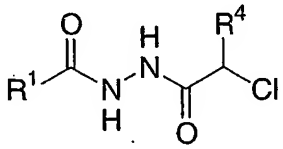
(IV)

to afford a compound of structural formula I.

In one embodiment of the process of the present invention, R^1 is trifluoromethyl and R^2-R^5 are hydrogen.

In another embodiment of the process of the present invention, the final product of the reaction sequence of structural formula I is isolated from the reaction mixture. In a further embodiment, the final product can be used without isolation for further chemical modification.

The first step in the process of the present invention entails the preparation of a bis-hydrazide of structural formula III:



(III)

This is accomplished by sequential acylation of hydrazine in one-pot with active esters, carboxylic acid anhydrides, and/or carboxylic acid chlorides. An aqueous solution of hydrazine, such as commercially available 35 wt. % solution in water, may be used for the acylation reactions. However, other forms of hydrazine may also be employed, such as hydrazine hydrate, hydrazine monohydrate, and anhydrous hydrazine. For example, in the case wherein R^1 is trifluoromethyl, hydrazine is reacted with ethyl trifluoroacetate in a suitable organic solvent to generate the mono-trifluoroacetylhydrazide which is then further reacted with R^4-substituted chloroacetyl chloride optionally in the presence of a base. Suitable organic

solvents for the bis-acylation reaction include acetonitrile, THF, DMF, diphenyl ether, toluene, ethylene glycol dimethyl ether, and ethylene glycol diethyl ether. Suitable bases include alkali hydroxides, such as sodium and potassium hydroxide; alkali hydrogencarbonates, such as sodium and potassium hydrogencarbonate; alkali carbonates, such as sodium and potassium carbonate; organic amines, such as pyridine, triethylamine and *N,N*-diisopropylethylamine; and alkali phenoxides, such as sodium phenoxide. The reaction is generally carried out at a temperature of about 0 °C to about 40 °C, but other temperatures may also be employed.

The subsequent step of the process of the present invention concerns cyclodehydration of a bis-hydrazide of structural formula III in the presence of a dehydration reagent optionally in the presence of a suitable organic solvent to afford the C-5 substituted 2-(chloromethyl)-1,3,4-oxadiazole of structural formula II. Suitable reagents to effect the cyclodehydration include phosphorous oxychloride ($POCl_3$); phosphorus pentoxide (P_2O_5); thionyl chloride; polyphosphoric acid (PPA); oleum; alkyl or aryl dichlorophosphites, such as methyl dichlorophosphite and phenyl dichlorophosphite; alkanecarboxylic acid anhydrides, such as acetic anhydride; and alkanesulfonic anhydrides, such as trifluoromethanesulfonic anhydride. A base such as pyridine and 4-dimethylaminopyridine (DMAP) may be added along with the dehydration reagent. The reaction may be performed neat or in the presence of a suitable organic solvent, such as acetonitrile, NMP, toluene, xylene, and mixtures thereof. The cyclodehydration reaction is carried out at a temperature of about 75 °C to about the reflux temperature of the reaction solvent. When acetonitrile is used as the reaction solvent, the reaction is carried out at the reflux temperature of the reaction mixture, namely about 81-82 °C. In one embodiment of this step of the present process, the dehydration reagent is neat $POCl_3$ or $POCl_3$ in acetonitrile.

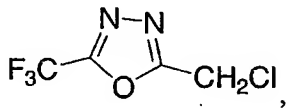
The third step of the process of the present invention concerns reaction of an ethylenediamine of structural formula V with a C-5 substituted 2-(chloromethyl)-1,3,4-oxadiazole of structural formula II in a suitable organic solvent to afford a cyclic amidine of structural formula IV. Suitable organic solvents for this transformation include alcoholic solvents, such as methanol, ethanol, and isopropanol, and mixtures thereof. This reaction is carried out at a temperature of about -30 °C to about 5 °C. If the reaction is carried out above about 5 °C, spontaneous cyclization of the amidine intermediate to afford the triazole of structural formula I may occur.

The final step of the process of the present invention concerns cyclodehydration of a cyclic amidine of structural formula IV to the final triazolopyrazine of structural formula I. This transformation is carried out in a suitable organic solvent at a temperature of about 45 °C to about the reflux temperature of the reaction solvent. Suitable organic solvents for this

transformation include alcoholic solvents, such as methanol, ethanol, isopropanol, n-butanol, and mixtures thereof. The addition of an acid or base accelerates the rate of the reaction. In the absence of added acid or base, the reaction requires heating in order to proceed at a reasonable rate. In the absence of added acid, the triazolopyrazine is obtained as a free base. When the reaction is carried out in the presence of an acid, the triazolopyrazine is obtained as an acid salt thereof. For example, the use of methanol with hydrochloric acid generates the hydrochloride salt and the use of methanol with acetic acid generates the acetate salt. Other salts of compounds of formula I may be obtained in a similar fashion using the appropriate acid in the final cyclodehydration step.

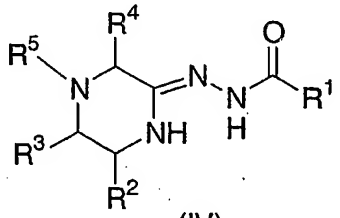
The process steps can be carried out without the need for isolating the intermediates of structural formulae II, III, and IV.

A further embodiment of this invention comprises the following novel compound which is an intermediate in the preparation of some of the compounds of structural formula I:



which is 2-(chloromethyl)-5-trifluoromethyl-1,3,4-oxadiazole.

Yet a further embodiment of this invention comprises the following novel compounds of structural formula IV which are intermediates in the preparation of the compounds of structural formula I:



(IV)

or an acid salt thereof, wherein

R^1 is optionally substituted phenyl or C_{1-4} alkyl unsubstituted or substituted with one to five fluorines; and

R^2, R^3, R^4 and R^5 are each independently hydrogen, C_{1-4} alkyl, or optionally substituted benzyl; or R^2 and R^3 taken together with the carbon atoms to which they are attached form a 5- to 7-membered cyclic aliphatic ring. In a class of this embodiment, R^1 is CF_3 and R^2-R^5 are hydrogen.

Representative experimental procedures utilizing the novel process are detailed below. The following Examples are provided for illustration purposes only and are not intended to limit the process of the present invention to the specific conditions for making these particular compounds.

Abbreviations: ACN is acetonitrile; DMF is *N,N*-dimethylformamide; EtOH is ethanol; IPAc is isopropyl acetate; MeOH is methanol; MTBE is methyl *t*-butyl ether; and NMP is N-methylpyrrolidinone.

By optionally substituted phenyl or benzyl is meant a phenyl or benzyl group which is unsubstituted or substituted with one to five substituents independently selected from the group consisting of halogen, cyano, nitro, trifluoromethyl, trifluoromethoxy, amino, hydroxy, carboxy, C_{1-4} alkyl, C_{1-4} alkoxy, and C_{1-4} alkylthio.

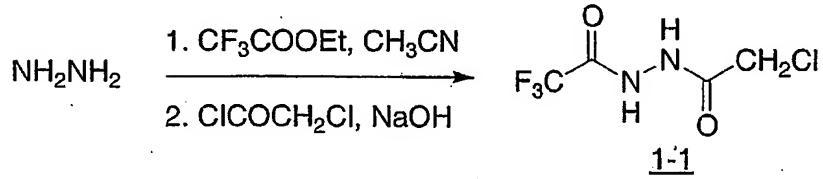
By halogen is meant fluorine, chlorine, bromine, or iodine.

The starting materials are either commercially available or known in the literature. Purification procedures include e.g., distillation, crystallization and normal or reverse phase liquid chromatography.

EXAMPLE 1

3-(Trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine, hydrochloride salt (1-4)

Step A: Preparation of bishydrazide (1-1)



1-1

Hydrazine (20.1 g, 35 wt% in water, 0.22 mol) was mixed with 310 mL of acetonitrile. 31.5 g of ethyl trifluoroacetate (0.22 mol) was added over 60 min. The internal temperature was increased to 25 °C from 14 °C. The resulting solution was aged at 22 - 25 °C for 60 min. The solution was cooled to 7 °C. 17.9 g of 50 wt% aqueous NaOH (0.22 mol) and 25.3 g of chloroacetyl chloride (0.22 mol) were added simultaneously over 130 min at a temperature below 16 °C. When the reaction was complete, the mixture was vacuum distilled to remove water and ethanol at 27 ~ 30 °C and under 26 ~ 27 in Hg vacuum. During the distillation, 720 mL of acetonitrile was added slowly to maintain constant volume

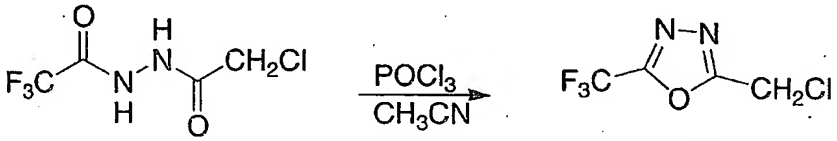
(approximately 500 mL). The slurry was filtered to remove sodium chloride. The cake was rinsed with about 100 mL of acetonitrile. Removal of the solvent afforded bis-hydrazide 1-1 (43.2 g, 96.5% yield, 94.4 area% pure by HPLC assay).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 4.2 (s, 2H), 10.7 (s, 1H), and 11.6 (s, 1H) ppm.

^{13}C-NMR (125 MHz, DMSO-d_6): δ 41.0, 116.1 (q, J = 362 Hz), 155.8 (q, J = 50 Hz), and 165.4 ppm.

HPLC conditions: Symmetry 4.6 x 250 mm C18 column; UV detection at 210 nm; mobile phase: 1:1 ACN: H_2O (0.1% H_3PO_4); flow rate: 1 mL/min; retention time of 1-1: 2.9 min.

Step B: Preparation of 5-(trifluoromethyl)-2-(chloromethyl)-1,3,4-oxadiazole (1-2)



1-1 1-2

Bishydrazide 1-1 from Step A (43.2 g, 0.21 mol) in ACN (82 mL) was cooled to 5 °C. Phosphorus oxychloride (32.2 g, 0.21 mol) was added, maintaining the temperature below 10 °C. The mixture was heated to 80 °C and aged at this temperature for 24 h until HPLC showed less than 2 area% of 1-1. In a separate vessel, 260 mL of IPAc and 250 mL of water were mixed and cooled to 0 °C. The reaction slurry was charged to the quench keeping the internal temperature below 10 °C. After the addition, the mixture was agitated vigorously for 30 min, the temperature was increased to room temperature and the aqueous layer was cut. The organic layer was then washed with 215 mL of water, 215 mL of 5 wt% aqueous sodium bicarbonate and finally 215 mL of 20 wt% aqueous brine solution. HPLC assay yield after work up was 86-92%. Volatiles were removed by distillation at 75-80 mm Hg, 55 °C to afford an oil which could be used directly in Step C without further purification. Otherwise the product can be purified by distillation to afford 1-2 in 70-80% yield.

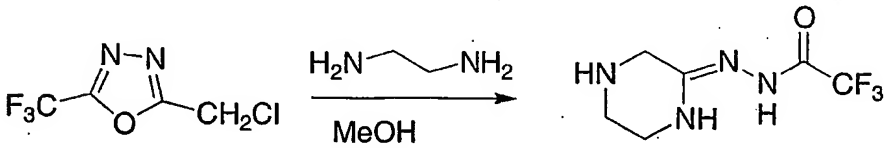
^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.8 (s, 2H) ppm.

^{13}C-NMR (125 MHz, $CDCl_3$): δ 32.1, 115.8 (q, J = 337 Hz), 156.2 (q, J = 50 Hz), and 164.4 ppm.

HPLC conditions: Symmetry 4.6 x 250 mm C18 column; UV detection at 210 nm; mobile phase: 1:1 ACN: H_2O (0.1% H_3PO_4); flow rate: 1 mL/min; retention time of

1-2: 8.8 min.

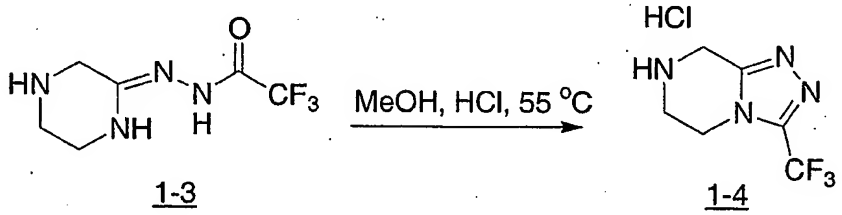
Step C: Preparation of N-[(2Z)-piperazin-2-ylidene]trifluoroacetohydrazide (1-3)



1-2 1-3

To a solution of ethylenediamine (33.1 g, 0.55 mol) in methanol (150 mL) cooled at –20 °C was added distilled oxadiazole 1-2 from Step B (29.8 g, 0.16 mol) while keeping the internal temperature at –20 °C. After the addition was complete, the resulting slurry was aged at –20 °C for 1 h. Ethanol (225 mL) was then charged and the slurry slowly warmed to –5 °C. After 60 min at –5 °C, the slurry was filtered and washed with ethanol (60 mL) at –5 °C. Amidine 1-3 was obtained as a white solid in 72% yield (24.4 g, 99.5 area wt% pure by HPLC). HPLC conditions: Symmetry 4.6 x 250 mm C18 column; UV detection at 254 nm; mobile phase: 5:95 ACN: H_2O (0.1% H_3PO_4); flow rate: 1 mL/min; retention time of 1-3: 2.1 min.

Step D: Preparation of 3-(trifluoromethyl)-5,6,7,8-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine, hydrochloride salt (1-4)



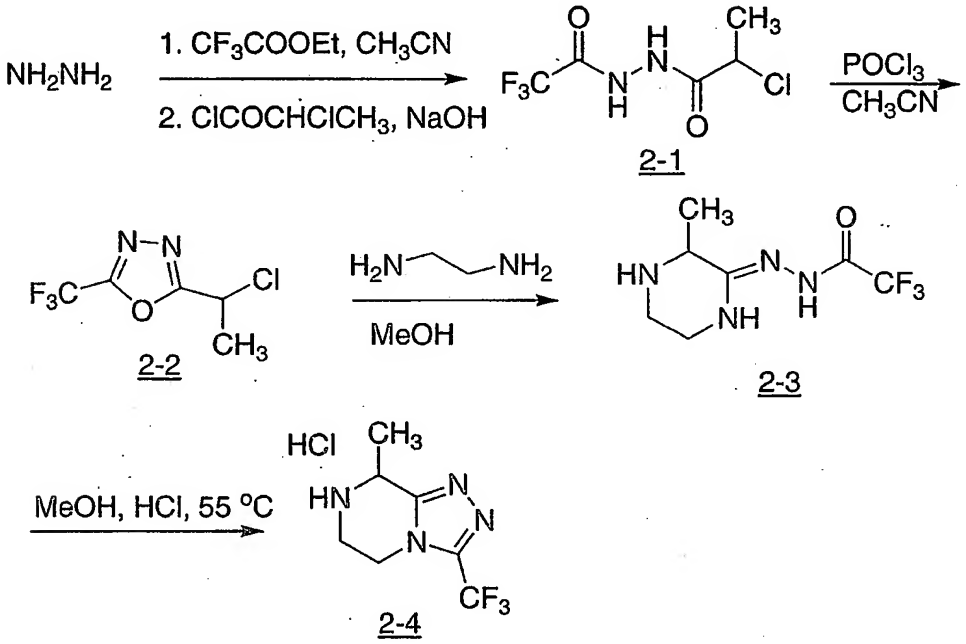
1-3 1-4

A suspension of amidine 1-3 (27.3 g, 0.13 mol) in 110 mL of methanol was warmed to 55 °C. 37% Hydrochloric acid (11.2 mL, 0.14 mol) was added over 15 min at this temperature. During the addition, all solids dissolved resulting in a clear solution. The reaction was aged for 30 min. The solution was cooled down to 20 °C and aged at this temperature until a seed bed formed (10 min to 1 h). 300 mL of MTBE was charged at 20 °C over 1 h. The resulting slurry was cooled to 2 °C, aged for 30 min and filtered. Solids were washed with 50

mL of ethanol:MTBE (1:3) and dried under vacuum at 45 °C. Yield of triazole 1-4 was 26.7 g (99.5 area wt% pure by HPLC); m.p. 264 °C (decomp); Electrospray mass spectrum: 192 (M+). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.6 (t, 2H), 4.4 (t, 2H), 4.6 (s, 2H), and 10.6 (b, 2H) ppm; ^{13}C-NMR (125 MHz, DMSO-d_6): δ: 39.4, 39.6, 41.0, 118.6 (q, J = 325 Hz), 142.9 (q, J = 50 Hz), and 148.8 ppm.

HPLC conditions: Symmetry 4.6 x 250 mm C18 column; UV detection at 210 nm; mobile phase: 1:1 ACN: H_2O (0.1% H_3PO_4); flow rate: 1 mL/min; retention time of 1-4: 2.5 min.

Scheme 2



EXAMPLE 2

8-methyl-3-(trifluoromethyl)-5,6,7,8,-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine, hydrochloride salt (2-4)

Step A: 2-chloro-*N'*-(trifluoroacetyl)propanohydrazide (2-1)

The procedure for the preparation of 1-1 was followed using 18.2 mL (201 mmol) of a 35 wt% aqueous solution of hydrazine, 24 mL (201.5 mmol) of ethyl trifluoroacetate, 20 mL (204.7 mmol) of 2-chloropropionyl chloride, and 16.4 g (205 mmol) of 50 wt% sodium hydroxide. After azeotropic removal of water and filtration of salts, a solution of 2-1 in 90 mL

of acetonitrile was obtained. Removal of solvent at reduced pressure afforded 2-1 as a white solid. Recrystallization was effected from acetonitrile; m.p. 160 °C; HRMS(ES+) calc. for $(M+Na)^+$: 240.9968, found: 240.9975; ^{1}H-NMR (400 MHz, CD_3OD): δ 1.68 (d, J = 7.5 Hz, 3H), 4.52 (q, J = 7.5 Hz, 1H), 4.85 (b, 2H); ^{13}C-NMR (100 MHz, CD_3OD): δ 20.5, 51.7, 115.0 (q, J = 280 Hz),156.3 (q, J = 40 Hz), 169.1.

Step B: 2-(1-chloroethyl)-5-(trifluoromethyl)-1,3,4-oxadiazole (2-2)

The procedure for the preparation of 1-2 was followed using 43.6 g (200 mmol) of 2-1 and 20 mL (218.5 mmol) of $POCl_3$ in 90 mL of acetonitrile. After aqueous workup, the brown oil obtained was purified by chromatography on silica gel to afford 2-2 as a colorless oil. HRMS(ES+) calc. for $(M+H)^+$: 201.0043, found: 201.0049; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.00 (d, J = 7 Hz, 3H), 5.23 (q, J= 7.0 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.9, 44.7, 116.0 (q, J = 270.0 Hz), 155.8 (q, J = 50.0 Hz), 167.6.

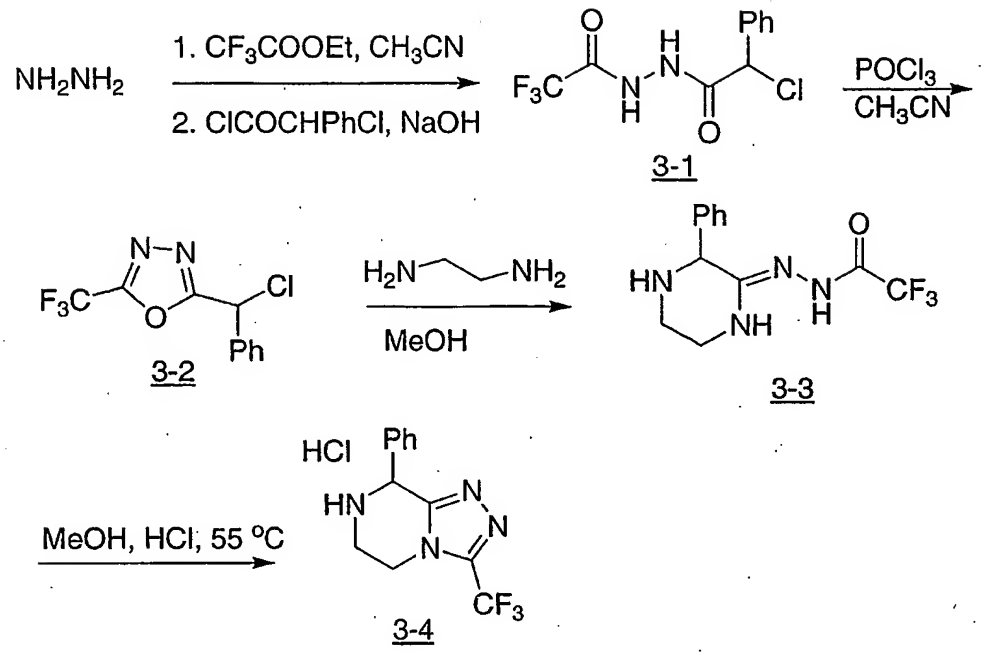
Step C: 2,2,2-trifluoro-*N*'-[(2Z)-3-methylpiperazin-2-ylidene] acetohydrazide (2-3)

The procedure for the preparation of 1-3 was followed using 1.0 g (4.99 mmol) of 2-2 and 1 mL (14.96 mmol) of ethylenediamine in 5 mL of methanol. After crystallization, 2-3 was obtained as a white solid; m.p. 141 °C (dec); MS (ES) 225 (M+H); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.31 (d, J = 7.5 Hz, 3H), 2.75-2.85 (m, 1H), 2.90-3.0 (m, 1H), 3.10-3.20 (m, 2H), 3.90 (qt, J = 7.5 Hz, 1H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 20.1, 37.7, 41.0, 46.9, 119.1 (q, J = 280.0 Hz), 156.3 (q, J = 30.0 Hz), 157.9.

Step D: 8-methyl-3-(trifluoromethyl)-5,6,7,8,-tetrahydro [1,2,4]triazolo[4,3-*a*]pyrazine, hydrochloride salt (2-4)

The procedure for the preparation of 1-4 was followed using 5.1 g (22.75 mmol) of 2-3 and 1.88 mL (23 mmol) of 37% hydrochloric acid. Removal of volatiles at reduced pressure afforded 2-4 hydrochloride salt as a colorless oily residue. HRMS(ES+) calc. for $(M+H)^+$: 207.0858, found: 207.0865; ^{1}H-NMR (400 MHz, CD_3OD): δ 1.90 (d, J = 7 Hz, 3H), 3.70-3.80 (m, 1H), 3.95-4.05 (m, 1H), 4.50-4.60 (m, 1H), 4.60-4.70 (m, 1H), 4.80 (b, 2H), 4.98 (q, J = 7 Hz, 1H); ^{13}C-NMR (100 MHz, CD_3OD): δ 14.8, 39.4, 40.7, 48.9, 118.1 (q, J = 270.0 Hz), 143.8 (q, J = 40.0 Hz), 151.5.

Scheme 3



EXAMPLE 3

8-phenyl-3-(trifluoromethyl)-5,6,7,8,-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine, hydrochloride salt (3-4)

Step A: *N'*-[chloro(phenyl)acetyl]-trifluoroacetohydrazide (3-1)

The procedure for the preparation of 1-1 was followed using 4.7 mL (51.8 mmol) of a 35 wt% aqueous solution of hydrazine, 6.2 mL (52.0 mmol) of ethyl trifluoroacetate, 10 g (52.9 mmol) of 2-chloro-2-phenylacetyl chloride and 4.25 g (53 mmol) of 50 wt% sodium hydroxide. After azeotropic removal of water and filtration of salts, a solution of 3-1 in 40 mL of acetonitrile was obtained. Removal of solvent at reduced pressure afforded 3-1 as a white solid. Recrystallization was effected from acetonitrile; m.p. 128 °C; HRMS(ES+) calc. for $(M+H)^+$: 281.0305, found: 281.0314; ^{1}H-NMR (400 MHz, CD_3OD): δ 4.86 (br, 2H), 5.60 (s, 1H), 7.30-7.50 (m, 3H), 7.50-7.65 (m, 2H); ^{13}C-NMR (100 MHz, CD_3OD): δ 58.2, 115.8 (q, J = 280 Hz), 127.7, 128.3(2C), 128.8(2C), 136.3,156.4 (q, J = 30.0 Hz), 167.5.

Step B: 2-[chloro(phenyl)methyl]-5-(trifluoromethyl)-1,3,4-oxadiazole (3-2)

The procedure for the preparation of 1-2 was followed using 16 g (57 mmol) of 3-1 and 5.7 mL (62.3 mmol) of $POCl_3$ in 40 mL of acetonitrile. After aqueous workup, the brown oil obtained was purified by chromatography on silica gel to give 3-2 as a pale yellow oil that crystallized on standing; m.p. 41 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.23 (s, 1H), 7.40-7.50 (m, 3H), 7.50-7.60 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 51.2, 116.0 (q, J = 270.0 Hz), 127.8, 129.3(2C), 130.1(2C), 133.9, 156.0 (q, J = 40.0 Hz), 166.4.

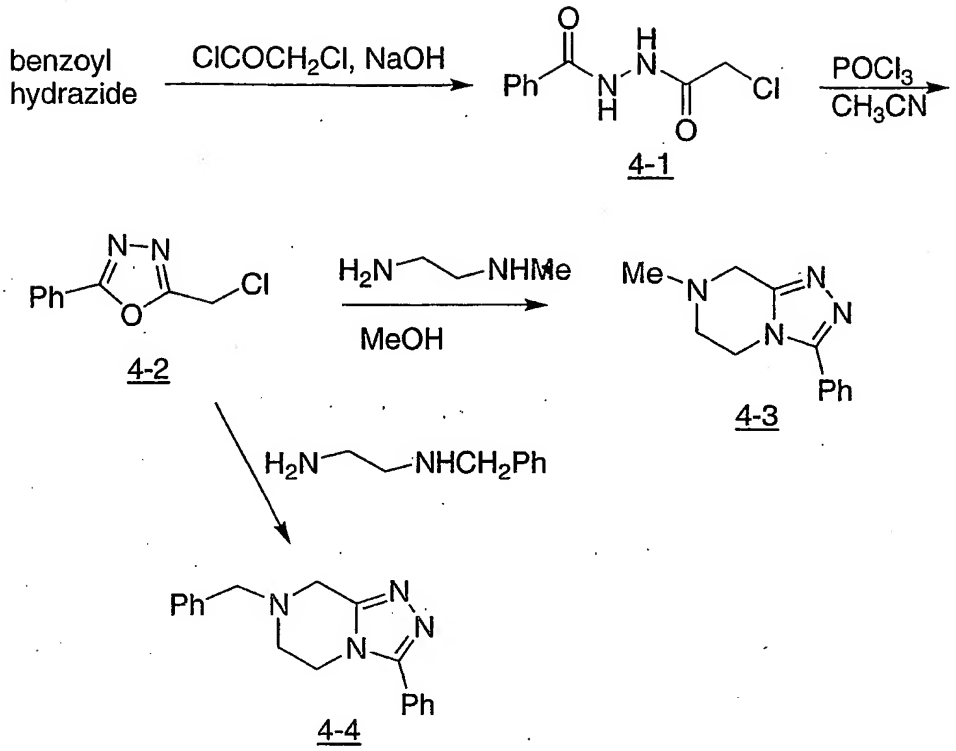
Step C: 2,2,2-trifluoro-*N*'-[(2Z)-3-phenylpiperazin-2-ylidene] acetohydrazide (3-3)

The procedure for the preparation of 1-3 was followed using 300 mg (1.14 mmol) of 3-2 and 0.38 mL (5.70 mmol) of ethylenediamine in 2 mL of methanol. After crystallization, 3-3 was obtained as a white solid; m.p. 141 °C (dec); MS (ES) 287 (M+H); HRMS(ES+) calc. for $(M+H)^+$: 287.1120, found: 287.1121; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.70-2.90 (m, 2H), 3.15-3.40 (m, 2H), 5.09 (s, 1H), 7.25-7.45 (m, 5H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 37.7, 40.8, 55.2, , 119.1 (q, J = 280.0 Hz), 128.2, 128.3, 128.8, 139.3, 155.0, 156.3 (q, J = 30.0 Hz).

Step D: 8-phenyl-3-(trifluoromethyl)-5,6,7,8,-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine, hydrochloride salt (3-4)

The procedure for the preparation of 1-4 was followed using 116 mg (0.41 mmol) of 3-3 and 40 μL (0.5 mmol) of 37% hydrochloric acid in 0.5 mL of methanol. Removal of volatiles at reduced pressure afforded 3-4 hydrochloride salt as a colorless oily residue; MS (ES) 269 (M+H); HRMS(ES+) calc. for $(M+H)^+$: 269.1014, found: 269.1016; ^{1}H-NMR (400 MHz, CD_3OD): δ 3.85-4.00 (m, 2H), 4.65-4.80 (m, 2H), 4.80-5.00 (b, 2H), 6.20 (s, 1H), 7.45-7.65 (m, 5H). ^{13}C-NMR (100 MHz, CD_3OD): δ 39.5, 40.8, 56.2, 118.1 (q, J = 270.0 Hz), 129.1, 129.6(2C), 130.6(2C), 131.0, 144.0 (q, J = 40.0 Hz), 150.3.

Scheme 4



EXAMPLE 4

7-methyl-3-phenyl-5,6,7,8,-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine (4-3)

Step A: *N'*-(2-chloroacetyl)benzohydrazide (4-1)

To a slurry of 40 g of benzoylhydrazide (294 mmol) in 320 mL acetonitrile were added simultaneously 23.6 mL of choroacetyl chloride (297 mmol) and 11.9 g of 50 wt% sodium hydroxide (297 mmol) while maintaining the internal temperature below 10 °C. After 30 min, the resulting slurry was filtered and the solids were washed with twice with 80 mL of water. Solids were dried under vacuum to afford 4-1 as a white solid; m.p. 165 °C; HRMS(ES+) calc. for $(M+Na)^+$: 235.0250, found: 235.0256; ^{1}H-NMR (400 MHz, DMSO-d6): δ 4.2 (s, 2H), 7.40-7.55 (m, 2H), 7.56-7.63 (m, 1H), 7.80-7.90 (m, 2H), 10.38 (s, 1H), 10.50 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d6): δ 41.3, 127.8, 127.9, 128.8, 132.3, 132.6, 165.7.

Step B: 3-(chloromethyl)-5-phenyl-1,3,4-oxadiazole (4-2)

The procedure for the preparation of 1-2 was followed using 40.3 g of 4-1 (190 mmol) and 19.5 mL of $POCl_3$ (208 mmol) in 200 mL acetonitrile at reflux for 4 h. After aqueous workup, volatiles were removed under reduced pressure to afford 4-2 as an off-white solid; m.p. 118 °C; HRMS(ES+) calc. for $(M+H)^+$: 195.0325, found: 195.0324; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.78 (s, 2H), 7.5-7.6 (m, 3H), 8.05-8.10 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 32.9, 123.2, 127.0, 129.0(2C), 132.1(2C), 162.1, 165.9.

Step C: 7-methyl-3-phenyl-5,6,7,8,-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine (4-3)

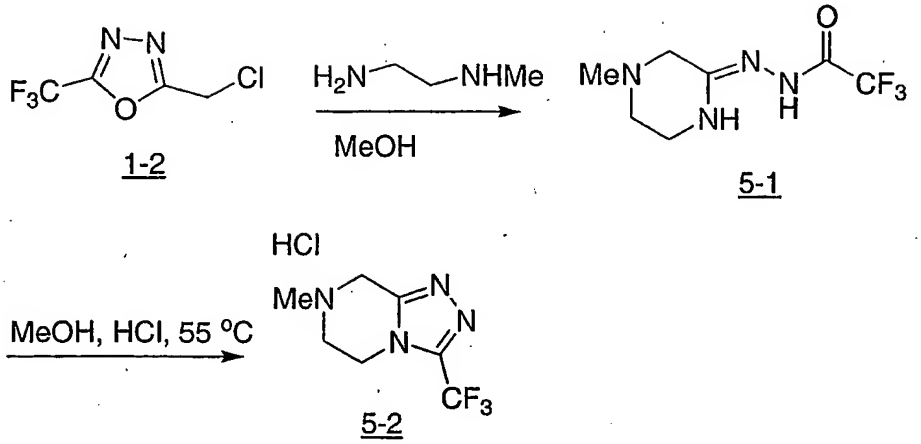
Oxadiazole 4-2 (2.0 g, 10.28 mmol) was combined with *N*-methylethylenediamine (1.52 g, 20.6 mmol) in 10 mL of methanol and the mixture warmed at 50 °C for 22 h. The brown solution was cooled to room temperature and the solvent removed at reduced pressure. The residue was dissolved in water and extracted with ethyl acetate 5 times. The organic extracts were combined, dried with magnesium sulfate and the volatiles were removed at reduced pressure to afford triazole 4-3 as a tan solid; m.p. 86 °C; MS (ES) 215 (M+H); HRMS(ES+) calc. for $(M+H)^+$: 215.1297, found: 215.1295; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.64 (m, 2H), 7.47-7.43 (om, 3H), 4.06 (t, J= 5.6, 2H), 3.80 (s, 2H), 2.79 (t, J= 5.6, 2H) 2.49 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 152.9, 150.4, 130.0, 129.0 (2C), 128.1 (2C), 127.0, 51.8, 51.6, 45.4, 44.0.

EXAMPLE 5

7-benzyl-3-phenyl-5,6,7,8,-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine (4-4)

Oxadiazole 4-2 (2.0 g, 10.28 mmol) was combined with *N*-benzylethylenediamine (3.1 g, 20.6 mmol) in 10 mL of methanol and the mixture warmed at 50 °C for 20 h. The brown solution was cooled to room temperature and the solvent removed at reduced pressure. The residue was purified by chromatography on silica gel to afford triazole 4-4 as a white solid; m.p. 102 °C; MS (ES) 291 (M+H); HRMS(ES+) calc. for $(M+H)^+$: 291.1610, found: 291.1618; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.84 (t, J = 6.5 Hz, 2H), 3.77 (s, 2H), 3.91 (s, 2H), 4.07 (t, J = 6.5 Hz, 2H), 7.2-7.8 (m, 10 H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 44.0, 49.0, 49.9, 61.7, 126.9, 127.7(2C), 127.9(2C), 128.5(2C), 128.8, 128.9(2C), 129.7, 136.7, 150.4, 152.7.

Scheme 5



EXAMPLE 6

7-methyl-3-(trifluoromethyl)-5,6,7,8,-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine, hydrochloride salt (5-2)

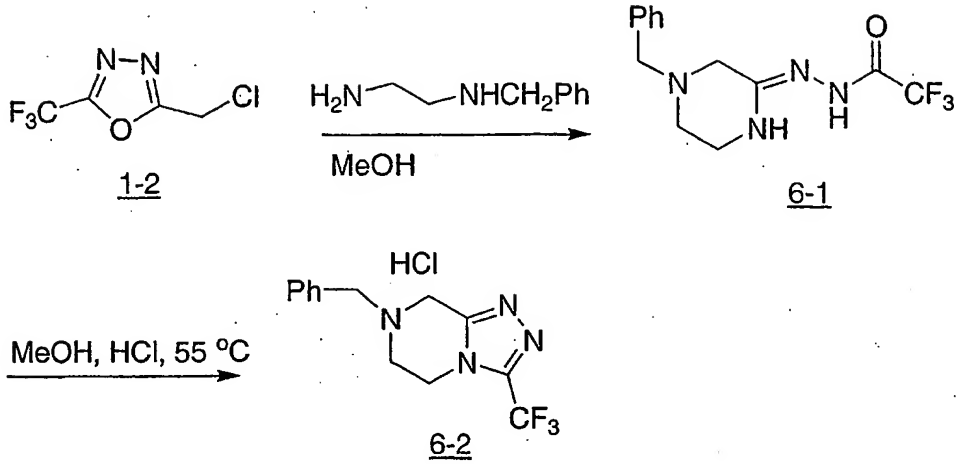
Step A: 2,2,2-trifluoro-*N'*-[(2Z)-4-methylpiperazin-2-ylidene] acetohydrazide (5-1)

The procedure for the preparation of 1-3 was followed with 2.07 g (11.1 mmol) of 1-2 and 1.65 g (22.26 mmol) of *N*-methylethylenediamine to afford 5-1 as a white solid; m.p. 139 °C (dec); MS (ES) 225 (M+H); HRMS(ES+) calc. for $(M+H)^+$: 225.0963, found: 225.0968; ^{1}H-NMR (400 MHz, DMSO-d6): δ 2.22 (s, 3H), 2.60 (t, J = 7.0 Hz, 2H), 3.26 (t, J = 7.0 Hz, 2H), 3.34 (s, 2H). ^{13}C-NMR (100 MHz, DMSO-d6): δ40.7, 44.7, 50.7, 51.7, 119.2 (q, J = 280.0 Hz), 152.8, 156.2 (q, J = 30.0 Hz).

Step B: 7-methyl-3-(trifluoromethyl)-5,6,7,8,-tetrahydro[1,2,4] triazolo[4,3-*a*]pyrazine, hydrochloride salt (5-2)

The procedure for the preparation of 1-4 was followed using 200 mg (0.89 mmol) of 5-1 and 73 μL (0.9 mmol) of 37% hydrochloric acid. After crystallization, 5-2 hydrochloride salt were obtained as a white solid; m.p. 175 °C; MS (ES) 207 (M+H); HRMS(ES+) calc. for $(M+H)^+$: 207.0858, found: 207.0860; ^{1}H-NMR (400 MHz, CD_3OD): δ 3.20 (s, 3H), 3.96 (t, J = 6.5 Hz, 2H), 4.63 (t, J = 6.5 Hz, 2H), 4.90 (s, 2H). ^{13}C-NMR (100 MHz, CD_3OD): δ 40.3, 41.9, 48.4, 49.1, 118.1 (q, J = 270.0 Hz), 143.7 (q, J = 40.0 Hz), 147.4.

Scheme 6



EXAMPLE 7

7-benzyl-3-(trifluoromethyl)-5,6,7,8,-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine hydrochloride salt (6-2)

Step A: *N'*-[(2Z)-4-benzylpiperazin-2-ylidene]2,2,2-trifluoroacetohydrazide (6-1)

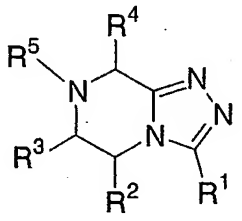
The procedure for the preparation of 1-3 was followed with 2.0 g (11.1 mmol) of 1-2 and 3.34 g (22.26 mmol) of *N*-benzylethylenediamine to afford 6-1 as a white solid; m.p. 138 °C (dec); MS (ES) 301 (M+H); HRMS(ES+) calc. for $(M+H)^+$: 301.1276, found: 301.1285; ^{1}H-NMR (400 MHz, DMSO-d6): δ 2.70 (t, J = 7.0 Hz, 2H), 3.30 (t, J = 7.0 Hz, 2H), 3.41 (s, 2 H), 3.58 (s, 2 H), 7.2-7.4 (m, 5H). ^{13}C-NMR (100 MHz, DMSO-d6): δ 40.6, 48.7, 49.7, 60.6, 119.0 (q, J = 280.0 Hz), 127.7(2C), 128.7(2C), 129.2, 137.4, 152.8, 156.4 (q, J = 30.0 Hz).

Step B: 7-benzyl-3-(trifluoromethyl)-5,6,7,8,-tetrahydro[1,2,4]triazolo[4,3-*a*]pyrazine, hydrochloride salt (6-2)

The procedure for the preparation of 1-4 was followed using 660 mg (2.2 mmol) of 6-1 and 180 μL (2.2 mmol) of 37% hydrochloric acid. After crystallization, 6-2 hydrochloride salt was obtained as a white solid; m.p. 215 °C; MS (ES) 283 (M+H); HRMS(ES+) calc. for $(M+Na)^+$: 283.1171, found: 283.1177; ^{1}H-NMR (400 MHz, CD_3OD): δ 3.92 (t, J = 6.5 Hz, 2H), 4.57 (t, J = 6.5 Hz, 2H), 4.68 (s, 2H), 4.74 (s, 2H), 7.5-7.6 (m, 3 H), 7.6-7.7 (m, 2H). ^{13}C-NMR (100 MHz, CD_3OD): δ 40.6, 46.5, 47.2, 59.7, 118.0 (q, J = 270.0 Hz), 128.2, 129.2(2C), 130.2(2C), 130.9, 143.6 (q, J = 40.0 Hz), 147.6.

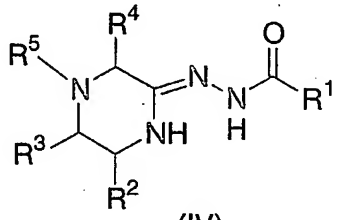
WHAT IS CLAIMED IS:

1. A process for preparing a compound of structural formula I:



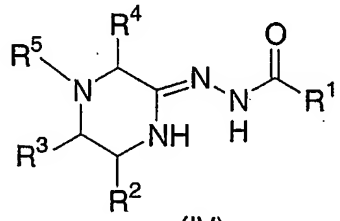
(I)

or an acid salt thereof, wherein
R^1 is optionally substituted phenyl or C_{1-4} alkyl unsubstituted or substituted with one to five fluorines; and
R^2, R^3, R^4 and R^5 are each independently hydrogen, C_{1-4} alkyl, or optionally substituted benzyl; or R^2 and R^3 taken together with the carbon atoms to which they are attached form a 5- to 7-membered cyclic aliphatic ring;
comprising the step of cyclizing a compound of structural formula IV in a suitable organic solvent



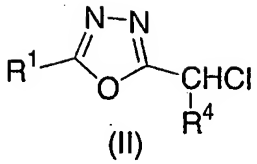
(IV)

2. The process of Claim 1 additionally comprising the step of producing a compound of structural formula IV:



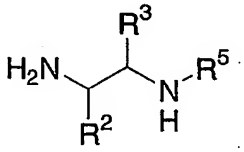
(IV)

by treating a compound of structural formula II:



(II)

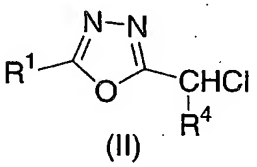
with an ethylenediamine of structural formula V:



(V)

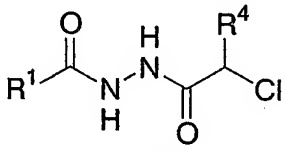
in a suitable organic solvent.

3. The process of Claim 2 additionally comprising the step of producing a compound of structural formula II:



(II)

by treating a compound of structural formula III:



(III)

with a dehydration reagent.

4. The process of Claim 1 wherein R^2-R^5 are hydrogen and R^1 is trifluoromethyl.

5. The process of Claim 1 wherein said acid salt is the hydrochloric acid salt.

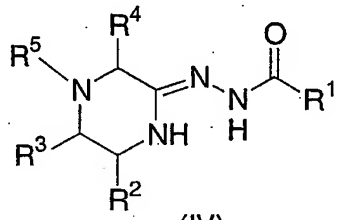
6. The process of Claim 1 wherein said organic solvent is methanol.

7. The process of Claim 3 wherein said dehydration reagent is phosphorous oxychloride.

8. The process of Claim 3 wherein said dehydration is carried out in the presence of a suitable organic solvent.

9. The process of Claim 8 wherein said organic solvent is acetonitrile.

10. A compound of structural formula IV:



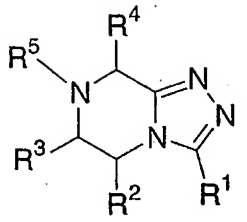
(IV)

or an acid salt thereof, wherein
R^1 is optionally substituted phenyl or C_{1-4} alkyl unsubstituted or substituted with one to five fluorines; and
R^2, R^3, R^4 and R^5 are each independently hydrogen, C_{1-4} alkyl, or optionally substituted benzyl; or R^2 and R^3 taken together with the carbon atoms to which they are attached form a 5- to 7-membered cyclic aliphatic ring.

11. The compound of Claim 10 wherein R^1 is trifluoromethyl and R^2-R^5 are hydrogen.

12. A compound which is 2-(chloromethyl)-5-trifluoromethyl-1,3,4-oxadiazole.

13. A process for preparing a compound of structural formula I:



(I)

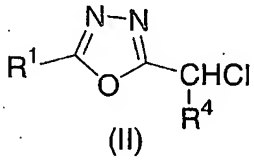
or an acid salt thereof, wherein

R^1 is optionally substituted phenyl or C_{1-4} alkyl unsubstituted or substituted with one to five fluorines; and

R^2, R^3, R^4 and R^5 are each independently hydrogen, C_{1-4} alkyl, or optionally substituted benzyl; or R^2 and R^3 taken together with the carbon atoms to which they are attached form a 5- to 7-membered cyclic aliphatic ring;

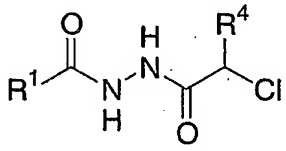
comprising the steps of:

(a) producing a compound of structural formula II:



(II)

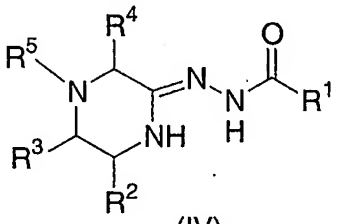
by treating a compound of structural formula III:



(III)

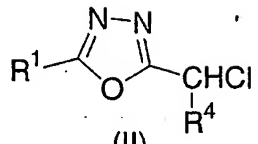
with a dehydration reagent;

(b) producing a compound of structural formula IV:



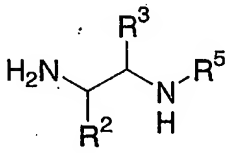
(IV)

by treating a compound of structural formula II:



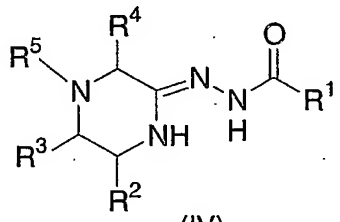
(II)

with an ethylenediamine of structural formula V in a suitable organic solvent



(V) ;

and (c) cyclizing a compound of structural formula IV in a suitable organic solvent



(IV)

to afford a compound of structural formula I.